ATTAINMENT: A phase Ib trial of MDX-124, a first-in-class annexin-A1 targeting antibody, alone and in combination with anti-cancer treatments, in patients with advanced solid tumors

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BACKGROUND

Annexin-A1 is a Ca^{2+}-dependent phospholipid binding protein that is secreted from both cancer and immune cells in response to several physiological stimuli. Extracellular annexin-A1 modulates cellular functions through interactions with formyl peptide receptors (FPR1/2) driving cancer cell growth[1], angiogenesis[2], migration[3] and drug resistance[4], as well as modulating the tumor microenvironment[5]. Overexpression of annexin-A1 has been observed in multiple cancer indications including pancreatic, triple-negative breast, colorectal, lung and prostate, correlating with poor prognosis and decreased overall survival[6-7].

SCIENTIFIC RATIONALE

MDX-124 is a first-in-class humanised IgG1 monoclonal antibody that specifically targets a unique epitope present on annexin-A1[8]. Pre-clinical studies have shown MDX-124 to have a multi-pronged anti-cancer mechanism of action (Figure 1). MDX-124 significantly reduces cancer cell growth, induces a G1 phase cell cycle arrest, inhibits tumor growth *in-vivo*, reduces metastasis and induces antibody-dependent cellular cytotoxicity in cancer cells which express annexin-A1[9-11]. Additionally, MDX-124 has demonstrated synergistic activity when combined with other anti-cancer therapies[10,12]. These data indicate blocking the action of annexin-A1 has anti-cancer and therapeutic activity.

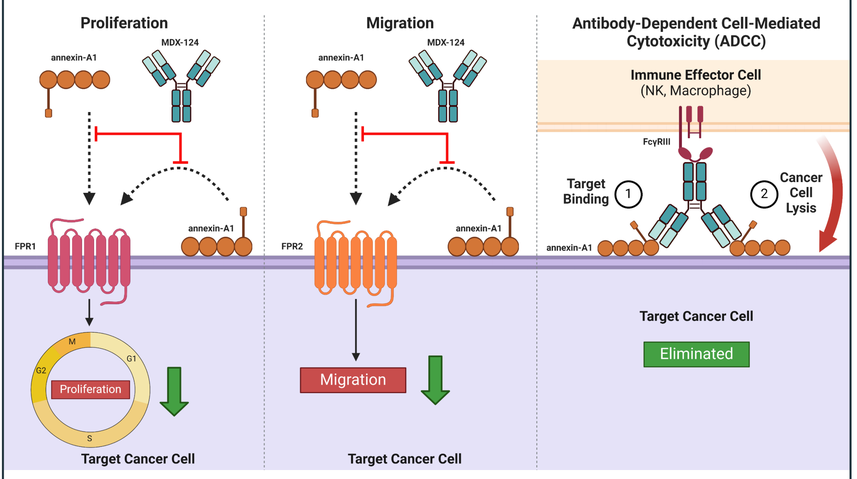

Figure 1. Proposed mechanism of action of MDX-124

OBJECTIVES

PRIMARY

- Determine RP2D of MDX-124 as a single agent and in combination with anti-cancer treatments.

SECONDARY

- Assess safety and tolerability of MDX-124 alone and in combination with anti-cancer treatments.
- Characterise the PK of MDX-124 alone and in combination with anti-cancer treatments.
- Assess evidence of anti-tumor activity of MDX-124 alone and in combination with anti-cancer treatments as per RECIST v1.1.

EXPLORATORY

- Explore the relationship between dose, blood borne and tissue biomarkers (e.g. circulating and/or tumoral expression of annexin-A1, immune cell infiltration).
- Assess host immune response to MDX-124 (immunogenicity and immunophenotyping).
- Assess circulating levels of annexin-A1 in participants at baseline and after dosing with MDX-124 to correlate with response and outcome.
- Analyse circulating annexin-A1 bound by MDX-124 after dosing to assess circulating annexin-A1 as a biomarker.

STUDY DESIGN

MODULE 1

- Recommended phase 2 dose (RP2D) of MDX-124 will be determined using a Bayesian Optimal Interval (BOIN) model enrolling up to 24 participants.
- Cohorts of 1 will be used initially but will increase to 3 in the event of a dose limiting toxicity (DLT) or if determined by the Dose Escalation Committee.
- MDX-124 is administered on day 1 of a 14-day cycle via intravenous infusion.
- Participants enrolled at lower doses will be given the option to be up-titrated to the next dose level.
- An additional 20 participants will be enrolled in an expansion cohort to explore 2 dose schedules.

MODULE 2

- Evaluate MDX-124 in combination with established standard of care (SOC) therapy.
- The Module 2 RP2D will be determined by using a standard '3 + 3' design. The dose of the SOC therapies will not be escalated.
- 20 participants will be treated at the RP2D.
- Arm 1 will evaluate front-line pancreatic cancer patients receiving MDX-124 in combination with gemcitabine and nab-paclitaxel.
- Biopsy will be performed at screening with an optional biopsy at the end of Cycle 2.
- A maximum of 3 additional tumor-specific arms will be added based on emerging clinical and non-clinical data.

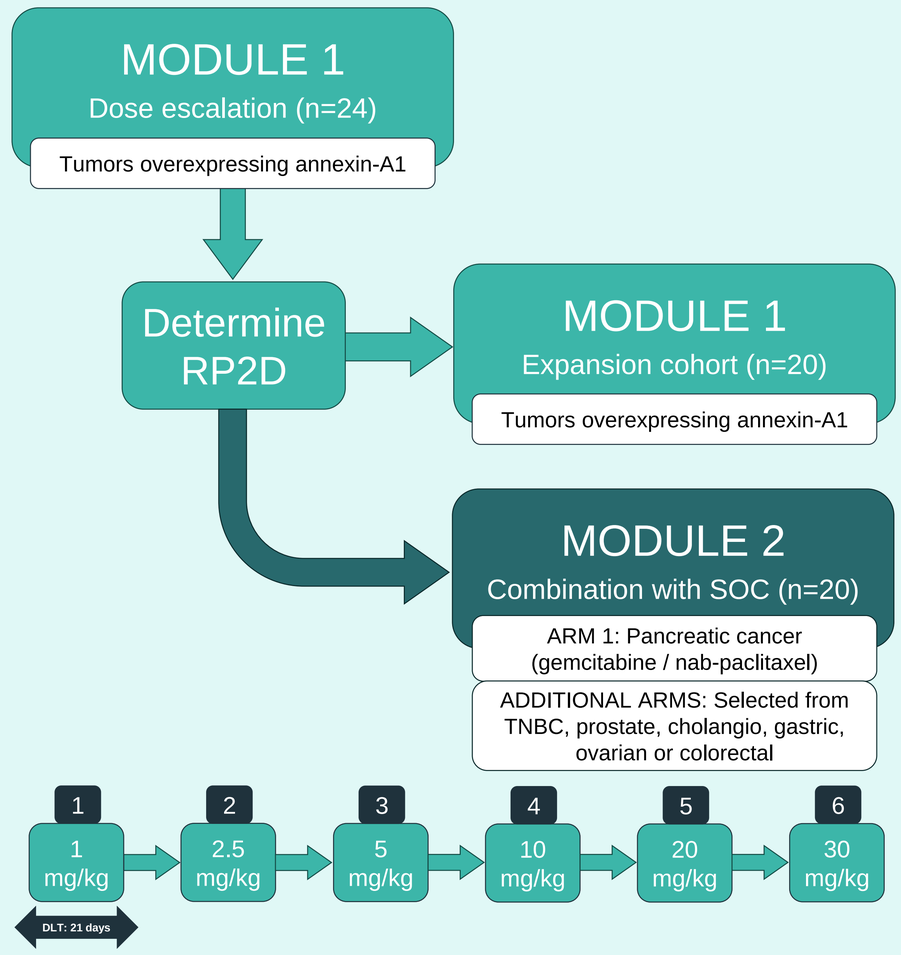

Figure 2. ATTAINMENT trial schema and Module 1 dose escalation plan

ELIGIBILITY

KEY INCLUSION CRITERIA

MODULE 1

- Adult patients (≥18 years) with ECOG performance score 0-1.
- Histologically or cytologically confirmed solid tumors believed to overexpress annexin-A1 which are not amenable to or refractory to standard therapy (e.g. pancreatic, triple-negative breast, liver, lung, prostate, cholangiocarcinoma, gastric, ovarian, colorectal, bladder).
- Participants must have measurable disease per RECIST version 1.1 criteria or evaluable disease.

MODULE 2

- Arm 1: Participants with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic cancer for which FOLFIRINOX treatment is not indicated and gemcitabine with nab-paclitaxel is the standard of care.
- Participants must be suitable for combination treatment.
- Participants must have at least one measurable lesion as per RECIST v1.1.

KEY EXCLUSION CRITERIA

MODULE 1

- Residual toxicities from chemotherapy or radiotherapy, which have not regressed to Grade ≤1 severity (per NCI CTCAE v5).
- History of another malignancy diagnosed within 2 years (except non-melanoma skin cancer, curatively treated carcinoma *in-situ* of the breast or cervix).
- Tumors identified as not responding to annexin-A1 inhibition such as head and neck (oral, nasal and throat) and cervical.
- Participant receiving daily high dose steroids (> 2 mg/day of dexamethasone or >15 mg/day prednisolone) during the 14 days prior to first dose of MDX-124.

MODULE 2

- Participant has received previous systemic anti-cancer therapy for advanced pancreatic adenocarcinoma. However, participants who have received adjuvant or neoadjuvant treatment which has been completed ≥ 6 months prior to registration are eligible.
- Participant has history of posterior reversible encephalopathy syndrome (PRES).
- Participant has history of (non-infectious) pneumonitis or has current pneumonitis.

MORE INFORMATION

For a copy of this poster or for more information on the 'ATTAINMENT' study please scan this QR code

CURRENT STATUS

The study began enrolling participants in August 2023 at multiple sites in the UK. Cohorts at 1, 2.5 and 5 mg/kg have been completed without any DLTs. Enrolment to cohort 4 (10 mg/kg) completed in April 2024. ***Clinical trial number***: ISRCTN78740398

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Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. May 31 – June 4, 2024 | **Abstract: TPS2671**